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09/491,982	01/27/2000	Stephen Shaughnessy	1171-101	9313

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EXAMINER
PRASAD, SARADA C

ART UNIT	PAPER NUMBER
1646	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/491,982	Applicant(s) SHAUGHNESSY ET AL.	
	Examiner Sarada C Prasad	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *19-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-41* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

1. Receipt of Applicants' arguments and amendments filed in Paper No. 10 (2/1/02) is acknowledged. New formal drawings submitted in Paper No. 11 (1/16/02) are also acknowledged.

Currently claims 1-41 are pending, and amendments to claims 1-18, 40-41 have been entered. Claims 19-39 are withdrawn from consideration as being non-elected, while claims 1-18, 40-41 are under consideration for examination.

2. The following previous objections/rejections are withdrawn in light of Applicants' amendments filed in Paper No. 10 (2/1/02).

(i) objections based on numbering of SEQ ID No. in the specification and claims;

(ii) objections based on bolded amino acids in Figure 3 and Figure 4;

(iii) objections based on missing sequence identifier in claim 5;

(iv) rejection of claims 1-18 under 35 U.S.C. 112-first paragraph based on recitation of 'a process of treating or alleviating the symptoms of a pathological condition in which bone density is decreased...' in claim 1;

(v) rejection of claims 1, 40, 41 under 35 U.S.C. 112-second paragraph based on recitation of 'acronyms';

(vi) rejection of claims 40, 41 under 35 U.S.C. 112-second paragraph based on recitation of 'a composition of matter...';

(vii) rejection of claim 13 under 35 U.S.C. 112-second paragraph based on recitation of an amino acid sequence without sequence identifier;

(viii) rejection of claims 40, 41 under 35 U.S.C. 112-second paragraph based on recitation of 'interaction';

(ix) rejection of claim 14 under 35 U.S.C. 112-second paragraph based on recitation of 'a small molecule..';

(x) rejection of claims 15 under 35 U.S.C. 112-second paragraph based on recitation of 'IL-11 antagonist..'.

3. Applicant's arguments filed in Paper No. 10 (2/1/02), have been fully considered but were deemed persuasive in part. The issues remaining and new issues, are stated below. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 first paragraph

4. Claims 2, 4, 11, 15-16 remain rejected under 35 USC § 112 first paragraph for reasons of record set forth in Paper No. 9 (7/16/01 as well as additional reasons stated as follows.

The factors considered when determining if the disclosure satisfies enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

4a. Claim 2 remains rejected based on broad recitation of '...an effective amount of a substance which inhibits....'.

The specification sets forth for use of IL-11 antibody, mutant IL-11R, IL-11R binding peptides, and soluble IL-11 peptides for use as antagonists of IL-11 (Examples 2, 4, 5) to inhibit formation of tertiary complex of IL-11, IL-11R and gp130 to achieve inhibition of reduction in bone density (pages 23-28 of specification). However, the term 'substance' is extremely broad that no conceivable compound is excluded from what can be covered by the term substance. Applicants assert that exemplary substances of widely varying classes that perform this function and would be expected to be useful in the presently claimed methods have been set forth (page 7, lines 15-19 of the specification), antibodies to IL-11, antibodies to IL-R, antibodies to gp130, mutant forms of Il-11 receptor, small molecule antagonists of IL-11, and peptide compounds which include sequences which selectively interact with IL-11 in the region normally bound by IL-11R, so as to interfere with the normal interaction between IL-11 and IL-11R.

Applicants request an explanation of the Examiner's reasoning based on the unpredictability of in vivo treatment using these substances, because their mechanism of action is unpredictable. First of all, the rejection is based on the scope of enablement of claim 2 as recited. The specification is enabling for the substances that are described in terms of their structure and function as in claims 5, 6, 7, 12, 13, 17, 18. However, the specification is non-enabling for 'any and all substances' that the claim language reads on. Secondly, function alone does not enable one of skill in the art to make and use the 'substances' claimed, because absent a correlative structure, or guidance regarding the structures that would predictably have the desired effect, it would require undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. One of skill in the art would require guidance as to which substances to select from, for example, in the instant case antagonizing IL-11 is intended in order

to inhibit the formation of tertiary complex of IL-11, IL-11R and gp130. It is possible that even changing ionic strength would be sufficient to disrupt or inhibit formation of the ternary complex or one might select analogous peptides of IL-11 or IL-11R or gp130 that would act as competitors during the process of binding interactions. Therefore, the range of substances that can be included in the claim language is extremely broad for one of skill in the art to practice the invention as claimed with any reasonable expectation of success, and therefore provides the reasoning for requirement of undue experimentation and the instant enablement rejection of claim 2 under 35 USC 112-first paragraph.

4b. Claim 4 remains rejected based on broad recitation of 'a mutant IL-11R'.

The specification sets forth for enablement with a mutant of IL-11R recited in claims 5-7. However, the specification is non-enabling for practice of instant claim with 'any and all' of the mutants of IL-11R. The applicants assert that 'one does not look to the claims but to the specification to find out how to practice the claimed invention MPEP 2164.08', and they therefore conclude that there is no need to test all possible mutations throughout the entire sequence of IL-11R to identify such substances that would be classified as mutants of IL-11R. The applicants also argue that the specification teaches how to make mutants. Applicant's arguments have been fully considered but they are not persuasive. The instant arguments are not found to be commensurate with the scope of claim 4.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). While instant specification is enabled for mutants commensurate in scope with claim 5 in which the region is identified, or mutations in the IL-11

binding region, that the instant specification does not provide sufficient guidance to render it predictable which mutations in any other region of the receptor would predictably share the instant activity.

4c. Claim 11 remains rejected based on broad recitation of 'wherein the substance is an IL-11 binding peptide'.

The applicants assert that they teach 3 classes of binding peptides, namely, SEQ ID NO. 6 (page 9, line 31), SEQ ID NO 9 (page 10, line 9), and SEQ ID NO. 1. This argument has been found to be persuasive. The specification is enabled for methods using peptides comprising any of those three sequences. However, Applicants' argument regarding use of the TRAP assay to screen for other peptides is not persuasive, because they have not provided any other structures what would predictably function in a similar manner to those of SEQ ID No. 6, 9, and 1.

4d. Applicants argument regarding the non-effective peptide 2, in Example 5, is not an IL-11 binding peptide is found to be persuasive.

4e. Claim 14 remains rejected based on broad recitation of 'a substance that is a small molecule no more than 30 kDa in molecular weight'.

The grounds of rejection of instant claim 11 are based on scope of enablement of the instant claim reciting 'a small molecules'. The nature of small molecules encompassed by instant claims with the limitation of a '30kDa small molecule' can be numerous, for example, a peptide, or a complex carbohydrate, or any compound whose structure is not contemplated in the specification. One of skill would not know which small molecule of 30 kDa or less to use for inhibiting the formation of ternary complex of IL-11, IL-11R and gp130. As stated above, in para 4a, limitations of the specification are not read into claims although claims are interpreted in

light of the specification. Absent a correlative structure of what is that '30 kDa small molecule' that would predictably have the desired effect, it would require undue experimentation for one of skill to practice the invention as claimed.

4f. Claims 15 remains rejected based on broad recitation of 'IL-11 antagonist'.

The grounds of rejection of this claim are scope of enablement using substances covered by the instant recitation because the intended IL-11 antagonist can be IL-11 antibody, or soluble IL-11 peptides that compete for binding to IL-11R or any other molecule that can potentially antagonize the biding of IL-11 to its receptor which might also include any antagonists whose structure is not contemplated in the specification. One of skill would not know which antagonist to use for inhibiting the formation of ternary complex. As stated above in para 4a, and 4e, limitations of the specification are not read into claims although claims are interpreted in light of the specification. Absent a correlative structure of what is the IL-11 antagonist that would predictably have the desired effect, it would require undue experimentation for one of skill to practice the invention as claimed.

4g. Claim 16 remains rejected based on broad recitation of 'IL-11R binding peptide'.

The grounds of rejection of this claim are scope of enablement using substances covered by the instant recitation of 'IL-11R binding peptide', because the variety of binding peptides encompassed by the claims language can include IL-11R antibodies, or mutant IL-11 peptides that can only bind but do not effect signal transduction whose nature 'is' or 'is not' contemplated in the specification. One of skill would not know which binding peptides to use for inhibiting the formation of ternary complex. As stated above in para 4a, 4e, and 4f, limitations of the specification are not read into claims although claims are interpreted in light of the specification.

The specification is enabling for the instant claims 17 and 18 reciting the antibodies as the IL-11 R antagonists which inhibit the interactions between IL-11 and IL-11R or IL-11R and gp130 respectively. However, absent a correlative structure of what the antagonists are that would predictably have the desired effect, it would require undue experimentation for one of skill to practice the invention as claimed.

In case of each of these instant claims 2, 4, 11, 14, 15, 16 the question of scope of enablement is one of how to 'make and use' and predictability of success. Absent some kind of structural information or guidance, one could not reasonably identify the molecules that 'would' predictably have the desired function and those that 'would not' and screening large numbers of compounds where the expectation of success is unpredictable due to the lack of adequate guidance amounts to undue experimentation.

It is believed that all of applicant's arguments have been addressed and based on the above discussion, predictability in the art, lack of sufficient guidance the 35 USC 112-first paragraph rejection of record is being maintained.

Claim Rejections - 35 USC § 112 Second paragraph

5. Claim 1 remains rejected under 35 USC § 112 second paragraph for reasons of record set forth in Paper No. 9 (7/16/01).

5a. Claim 1 remains rejected based on omitting a positive recitation of a method step for inhibiting the formation of a tertiary complex of IL-11, IL-11R and gp130, because it is not clear as to what is to be done for achieving inhibition of complex formation. For example, one of skill in the art would not know what is to be administered to achieve the desired result.

Applicants assert that claim 1 is a broad generic claim in which the only method step is 'inhibiting the formation of tertiary complex...' and is not indefinite, and that it encompasses any means of inhibiting formation of the ternary complex (page 15, entire 3rd para). This argument is not found to be persuasive because the relationship between inhibition of formation of ternary complex , and inhibition of reduction of bone density is not clearly established within the claim. Additionally, neither is the mechanism by which the inhibition of complex formation is intended to be accomplished.

New objections:

5b. Claims 40-41 are objected to based on recitation of 'bindings' rather than 'binding' because 'bindings' is not the plural term of 'binding' unlike for 'interactions' for 'interaction'.

Claim Rejections - 35 USC § 102

6. Claims 1-5, 10-11, 15-16, 40-41 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO9619574 for reasons of record set forth in Paper No. 9 (7/16/01).

Instant claims 1-5, 10-11, 15-16, 40-41 are directed to a method of inhibiting reduction of bone density in a mammalian patient having a pathological condition in which bone density is decreased, comprising inhibiting the formation of a tertiary complex in the patient of IL-11, IL-11R and gp130. Teachings of WO9619574 citing '... inhibition of binding of IL-11 to the human IL-11R in a mammalian subject .....administering a therapeutically effective amount of a composition containing a human IL-11R protein, an IL-11R inhibitor or an antibody to a human IL-11R protein...and treating and preventing loss of bone mass in a mammalian subject ... ' (paragraphs bridging pages 6-7) have been used in the rejection of record.

The Applicants assert that 'WO9619574 is non-enabling in terms of treating or alleviating the symptoms of a pathological condition in which bone density is decreased in a mammalian patient (in vivo) suffering from such a condition' (Paper No.10, page 16, entire last para). Applicants also assert that in certain instances, in vitro data may not reliably predict in vivo effects as in case of IL-11..... and cite the reference of Nandurkar et al. which demonstrates differences between in vivo data and in vitro effects (entire page 17 of Paper No. 10). These arguments have been fully considered, however are not found to be persuasive for the following reasons:

(i) Nandurkar et al. do not discuss the role of IL-11 in either osteoclast development or bone resorption. But rather address the role of IL-11 receptor signaling in adult hematopoiesis, emphasize the pleiotropic nature of IL-11 as a growth factor with prominent effects on megakaryopoiesis and thrombopoiesis, and disclose its multiple roles in hematopoeitic compartment, in particular (paragraphs bridging columns 1 and 2 on page 2148);

(ii) Nandurkar et al. summarize the multiple roles of IL-11 with the statement 'it also acts on other organ systems, ...influences osteoclast development' while citing references of Girasole et al. and Romas et al. which support of the role of IL-11 in osteogenesis (page 2148, column 2, last 6 lines of 1st paragraph). In fact, it is the same reference of Romas et al. that has been applied for the instant 35 USC 103 rejection of instant claims. Therefore, Nandurkar et al. does not in any way teach away from the role of IL-11 in osteoclast development or bone resorption.

At the same time, the disclosure of WO9619574 provides the concept (paragraphs bridging pages 6-7), and methods to achieve the results (Examples 1-3 in pages 22-29, and citations of other prior art in page 16 last para). Furthermore, WO9619574 also teaches a variety of biological activities of the human IL-11R that would anticipate use of such IL-11R molecules to serve as antagonists of IL-11 binding to IL-11R (starting 2nd para of page 9-end of 3rd para of page 10), also points out instances where such inhibition may be beneficial (starting 2nd para of page 16-2nd para of page 17) as in treatment of postmenopausal osteoporosis (last phrase in page 16), including pharmaceutical compositions comprising IL-11R, IL-11R antibody, which support evidence of knowledge of the role of IL-11 in bone formation, and thus enablement of the WO9619574, thus anticipating instant claims 1-5, 10-11, 15-16, 40-41.

Based on the above discussion, the 35 USC102 (b) rejection of claims 1-5, 10-11, 15-16, 40-41 of record is being maintained.

Claim Rejections - 35 USC § 103

7. Claims 1-5, 10-11, 15-16, 40-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO9619574 in view of Romas et al. (1996) as set forth in Paper No. 9 (7/16/01).

The obviousness rejection of record of instant claims is based on the combined teachings of WO9619574, and Romas et al. suggesting the antagonists of IL-11 and IL-11R would be beneficial in the treatment of osteoporosis or bone loss.

Applicants assert that WO9619574 is non enabling for in vivo methods of treatment (page 16, entire last para, Paper No. 10); in vitro data does not predict in vivo data, and the role

of IL-11 in the hematopoetic system is unclear and cite Nadurkar et al. in support of their arguments. Applicants also assert that disclosure of WO9619574 just provides a conclusory prediction without any experimental support (neither in vitro nor in vivo), ..., a skilled artisan would not, a priori, have a reasonable expectation that antagonism of IL-11 would produce any effect in vivo. (page 17 of Paper No. 10 in its entirety).

However, these arguments are not found to be persuasive for the following reasons: In fact, Nadurkar et al., cited by the applicants as evidence against a supporting role of IL-11 antagonists in inhibiting bone resorption, do not address the role of IL-11 in bone resorption. Teachings of Nadurkar et al. address the multiple roles of these cytokines in different systems and explain why activity within the hematopoeitc system is not reflective of the activity in bone resorption. In fact, the success of the method requires only inhibition of the ternary complex formation, which would likely occur regardless of the activity of other cytokines. Furthermore, WO9619574 cites additional references disclosing how IL-11 and IL-11R may play a role in the regulation of maturation and repair and point out human IL-11R protein and IL-11R inhibitors may be useful in treatment of bone loss associated with osteoporosis, postmenopausal osteoporosis..... (Paragraphs bridging pages 16-17), thus confirming the evidence of the knowledge of IL-11's role in bone formation cited in the prior art.

Applicants also assert that Romas et al. teaches that IL-6 and IL-1 are also involved and would compensate for IL-11 (page 17 of Paper No. 10, 1st para, last 4 lines). Yet, Romas et al. have not provided any evidence of compensation by IL-6 or IL-1. Also, Romas et al. state that their results suggest a central role of gp-130 coupled cytokines, especially IL-11, in osteoclast

development; since osteoblasts and mature osteoclasts expressed IL-11 mRNA, both bone-forming and bone-resorbing cells are potential targets of IL-11 (abstract, last three lines).

Therefore, at the time the invention was made, one of skill in the art had ample motivation and reasonable expectation of success that antagonizing IL-11 would be beneficial for inhibition of bone loss from the combined as well as individual teachings of WO9619574 and that of Romas et al. thus rendering instant claims 1-5, 10-11, 15-16, 40-41 obvious.

Conclusion

8. No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
April 22nd, 2002

Yvonne Eyler

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